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THE CLINICAL RESULTS FROM THE USE OF SALVARSAN.*

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The intense interest in salvarsan that has been shown by the medical profession is only comparable to the enthusiasm created by the introduction of Koch's tuberculin. No new remedy has ever been given such an extensive preliminary trial in hospitals before being put upon the market. In all fairness to Ehrlich's preparation it must be said that most of the numerous communications upon the subject deal with the result of a single injection. It is not impossible that repeated doses with new or combined methods of technique may add to the efficacy of the remedy. More than enough investigation, however, has already been devoted to salvarsan to show its probable field of usefulness as well as its limitations and its dangers.

In discussing the clinical results from the use of salvarsan in syphilis the following important questions are suggested: How rapidly do the symptoms subside after the injection and how permanent is the action of the new drug? How do the results compare with those obtained by the use of mercury and potassium iodide? What are its unpleasant or dangerous effects, and what is the most efficacious method of its administration? In attempt-

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ing to answer these questions we are depending as far as possible upon our experience with fifty cases (most of them treated in the service of Dr. George Henry Fox at the New York Skin and Cancer Hospital), upon numerous other cases that we have seen in New York, and to a less extent upon the literature of the subject.

Every observer who has had a moderate experience with salvarsan must admit that in certain cases at least the new remedy has a powerful action in causing the disappearance of syphilitic manifestations. This symptomatic action is often strikingly shown in lesions of the mucous membranes, mucous patches, for instance, disappearing at times in from twelve to twenty-four hours. Since the drug, furthermore, causes a rapid covering of the chancre with epithelium, its employment should prove of great value where it is desired to lessen as quickly as possible the danger of infecting others. Its action in causing the disappearance of the induration in the chancre and lymphatic glands is slow and unsatisfactory.

The effect of salvarsan upon early cutaneous syphilides is only moderately rapid. In the case of the large, flat, papular syphilides it is generally admitted to be slow, a fact that certainly coincides with our own observations. Its effect upon the macular and upon the small, flat, and miliary papular syphilides is generally conceded to be somewhat quicker. Even in these forms of cutaneous syphilis we would certainly not call its action very brilliant. In the later cutaneous manifestations we have seen some excellent results comparable to those which have been reported by many other observers.

It is, perhaps, in the malignant precocious type of the disease that the most brilliant results have

been obtained. The new remedy has also shown its value in severe cases of syphilis that have proved refractory to mercury. A marked example of such a case (reported by Kakels) was a patient that one of us had formerly treated at the German Hospital. Previous to treatment with salvarsan he had been given vigorous inunctions of mercury and injections of atoxyl with little or no benefit.

The action of salvarsan is furthermore of value in the cases, actually very few in number, in which mercury cannot be tolerated. Such a case was reported by us in the *Journal of the American Medical Association* of March 4, 1911, p. 650, in which the patient who had previously been treated by an experienced syphilologist had found it impossible to take mercury by mouth, injection, or inunction. Indeed, under the administration of mercury he had suffered from necrosis and loss of a considerable portion of his gums. After two injections of salvarsan the lesions had practically healed.

Good results are reported from the use of salvarsan in congenital syphilis, our own experience in these cases, however, being very limited. Certainly no better results could be desired than that reported by Samuel W. Lambert in a case of infantile syphilis. The child who presented extensive macular and bullous lesions, hoarse voice, coryza, and enlargement of the liver and spleen, was given an injection of twenty-five milligrammes. At the end of three weeks the symptoms had entirely disappeared. In cases of parenchymatous keratitis in older children, the results, according to foreign observers, have been very unsatisfactory. While it is true that syphilitic sucklings have been benefited by the treatment of the mother alone, it would seem to be advisable to follow Ehrlich's suggestion to treat both mother and child independently.

Satisfactory results have been obtained in the treatment of active syphilis of the nervous system, while in the parasyphilitic affections, such as tabes and paresis, its effects have been found to be of little or no value. Fordyce has treated eighteen cases of tabes and considers the results to be discouraging. In several of the cases there was, however, marked improvement in the pains, which had previously been very distressing.

The action upon the Wassermann reaction should be included among the clinical symptoms, and be considered as a means of the greatest importance in determining the ultimate value of the new remedy. As the subject is, however, specially discussed by two other speakers it will be omitted in this paper.

The action of salvarsan upon the *Spirochæta pallida* has been found by a large number of observers to be very energetic. In the majority of cases the organisms disappear from the various lesions in from twelve to twenty-four hours. In one of our cases the spirochætæ disappeared at the end of seventy-two hours, in four others at the end of forty-eight hours. The powerful action upon the spirochætæ is well illustrated in two hopeless cases of infantile syphilis reported by Herxheimer and Reinke. One of these infants died at the end of two days, the other at the end of four days after injection. At the autopsy no spirochætæ could be found in any of the internal organs except the lungs, where they were present in agglutinated and degenerated forms.

Enough has been said to show that in causing the disappearance of syphilitic manifestations salvarsan has a marked and often brilliant action. The question as to the permanence of its action is one that is more difficult to answer.

The number of relapses that are reported in increasing numbers as more time elapses have largely destroyed the hope that syphilis might be cured by a single injection. A letter recently sent out by the *Medizinische Klinik*, requesting information upon the number of relapses that were being obtained, elicited the information from various observers, based upon 4,766 cases, that only 207 relapses had occurred. Judging from our own experience and from the cases of others that we have seen, this number would appear to be rather low. We feel confident that as these cases are further followed a much larger proportion of relapses will have to be recorded. In order to obtain any true idea as to the permanent action of salvarsan in syphilis, it will be necessary to carefully follow the cases for a number of years. It is not sufficient that the Wassermann reaction should become negative, or even remain so for six months or more. It is well known that a negative Wassermann reaction obtained in the first year or two in cases of syphilis treated by mercury is of comparatively little value. Certainly no one at the present time would think of saying that such a result meant a cure of syphilis.

In judging of the value of salvarsan fairness demands that it should be rigidly compared with two other remedies, whose value is universally recognized, namely, mercury and potassium iodide. There seems to be little doubt that in the enthusiasm that has followed the introduction of salvarsan, some observers have forgotten that in many cases equally good or better results could have been obtained by mercury. We agree in the main with the opinion expressed by Fisher, who writes that "no one seems to appreciate how rapidly syphilis may subside under ordinary treatment. Clinicians are surprised

by the rapidity of the action of '606,' when, if they should keep records of the cases in which it was used alone, they would find that syphilis disappears as fast or even faster under mercury." While this seems to be true of the majority of syphilitic mani-



FIG. 1.—Serpigenous syphilide of four months' duration.

festations, we feel convinced that in lesions of the mucous membranes at least the action of salvarsan is much more rapid than that of mercury. Furthermore, we do not agree with Fisher that the new

remedy should be solely reserved for cases that are refractory to mercury.

A comparison of the permanence of the action of salvarsan and mercury, judged by the occurrence



FIG. 2.—The same patient as Fig. 1, four weeks after one injection of 0.5 gramme of salvarsan.

of relapses, has certainly given us the impression that a thorough course of mercurial treatment gives much more lasting results than one or perhaps two injections of salvarsan. The relapses that we have

noted after injections of salvarsan have occurred at a discouragingly early period, e. g., three and four weeks. It must be admitted that mercury cannot abort syphilis (after the first few hours), can-



FIG. 3.—Ulcerating syphilide.

not prevent the chronic intermittent tendency to relapses, and cannot with certainty prevent the later occurrences of parasyphilitic affections. Whether salvarsan will be able to accomplish any of these greatly to be desired results is a problem for the future to decide.

The question of the danger and possible ill effects from the use of salvarsan is fully as important as the question of the good that it may accomplish. It is true that deaths have been reported, and that



FIG. 4.—Showing patient of Fig. 3, four weeks after one injection of 0.4 gramme of salvarsan.

other deaths have occurred which have not been reported. It is also true that in most of these fatal results the injections were given in cases in which the drug was, according to our present knowledge,



FIG. 5.—Gumma of four months' duration.



FIG. 6.—Showing condition of patient of Fig. 5, four weeks after one injection of 0.45 gramme of salvarsan.

contraindicated. In the very large number of injections that have been given with this new remedy, the serious effects are proportionately small. It cannot, however, be said that the use of salvarsan is entirely devoid of danger.

In regard to the possibility of causing blindness from optic atrophy such as that which formerly occurred from the use of atoxyl and arsacetin it must be admitted that the results have shown an agreeable disappointment. Finger's case of optic atrophy appears to have been the only one that has followed the use of salvarsan, and in this instance the patient had previously been given thirty injections of arsacetin and eighteen of enesol, e. g. preparations containing arsenic. It is true, however, that injections of salvarsan have been followed in a number of cases by various lesions of the eye and by nerve deafness. As to whether these lesions should be considered as relapses occurring in the course of the disease, or whether they are directly caused by the action of the drug, is difficult to decide.

The undesirable effects of the injection vary according to the method employed. The subcutaneous injections of a neutral suspension have now been practically given up owing to the possibility of necrosis. The effect of an intramuscular injection of an alkaline solution is also at times very painful and frequently followed for days or even weeks by distressing induration. The local effect of an oily suspension given in the buttocks, is, as a rule, well borne, especially when the injection is followed immediately by vigorous massage. A properly given intravenous injection should not be followed by any unpleasant local disturbances.

The general bye effects that follow the use of salvarsan are varied and include some of the following

symptoms: Rise of temperature, increase or diminution of the pulse rate, general malaise, headache, dizziness, sleeplessness or somnolence, epileptiform attacks, disturbance of vision, abdominal pains, vomiting, jaundice, excessive sweating, albuminuria, retention of urine, obstinate constipation, diminution or absence of skin and deep reflexes, paralyses, and herpes zoster. Formidable as these symptoms may appear they are as a matter of fact mostly of a very transitory nature and seldom at all alarming. Many of them have been observed in our cases. In one of our patients an abdominal herpes zoster developed forty-four days after injection. In only one case did we note the occurrence of the so called Herxheimer reaction in which the eruption appeared darker and more extensive on the day following the injection.

As an offset to some of the disagreeable bye effects of salvarsan may be mentioned its powerful tonic action in many cases of syphilis. We have repeatedly seen a marked improvement in the patient's general appearance, color, appetite, and mental attitude, following an injection of salvarsan. An increase in weight is also frequently observed, one of our patients having gained ten pounds in a month after treatment. The tonic action of the new remedy contrasts favorably with the depressing effects of mercury that are so often observed.

The question as to the most efficient method of administration of salvarsan has not as yet been settled. We would feel entirely satisfied with the intramuscular injection of an alkaline solution if it were not for the pain and induration that so often follows this method. We are convinced that the injection of oily suspensions are too slow in their action and are inclined to think that the effect of the intravenous injection is too ephemeral. Theoreti-

cally the best plan would seem to be to give an intravenous injection, followed in a few days by an intramuscular injection of an oily suspension. We have therefore recently adopted this plan and intend for the present at least to treat our patients in this manner.

CONCLUSIONS.

1. Salvarsan is unquestionably a remedy of great power in causing certain manifestations of syphilis to disappear.

2. Its symptomatic effect is perhaps most strikingly shown in lesions of the mucous membranes.

3. It seems to be of particular value in malignant precocious syphilis, in threatening destructive processes, and in cases that are refractory to mercury.

4. A final opinion as to the permanence of its action can only be given after a lapse of several years during which time both clinical manifestations and Wassermann reaction must be carefully observed.

5. Relapses are frequent and seem to occur more frequently than after treatment with mercury.

6. Except in certain selected cases we do not think that salvarsan will replace the use of mercury.

7. The disagreeable by effects from its use have in our experience been generally transitory and of little importance.

8. According to our present knowledge the most efficacious form of administration appears to be an intravenous injection followed in four days or later by an intramuscular injection of an oily suspension.

